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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/714,452	11/14/2003	R. Shoshana Bamdad Shendelman	M1015.70046US01	9378

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EXAMINER	
ANDERSON, JAMES D	
ART UNIT	**PAPER NUMBER**
1614	

DATE MAILED: 10/26/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/714,452	SHENDELMAN ET AL.	
	Examiner	Art Unit	
	James D. Anderson	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 July 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4* is/are pending in the application.

4a) Of the above claim(s) *1 and 2* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3-4* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' arguments, filed 7/24/2006, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous Office Actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

The examiner for the present application has changed. The new examiner is James D. Anderson. Contact information is provided at the end of this Office Action.

Status of the Claims

Claims 1-4 are currently pending. Claims 1-2 are withdrawn from further consideration (see below). Claims 3-4 are under examination and are the subject of this Office Action.

Election/Restrictions

Claims 1-2 are withdrawn from further consideration pursuant to 37 CFR § 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 7/24/2006.

Applicant's election with traverse of Group II, claims 3-4 in the reply filed on 7/24/2006 is acknowledged. The traversal is on the ground(s) that groups I and II are closely related that it would not present an undue burden on the examiner to search them together. This is not found persuasive because the patient populations of groups I and II are different and would require

different searches. For example, the claims of group I are drawn to the treatment of any invasive cancer, whereas the claims of group II are drawn to the treatment of patients where angiogenesis inhibition is indicated. Thus, the claims of group I are drawn to a different patient population than those of group II, including the treatment of invasive cancers where angiogenesis inhibition is not indicated (as required by the patients of Group II). Further, the patients of group II include those with benign tumors, thus further distinguishing them from the patients of group I. As such, the characterization of the patients of groups I and II is different and would require a different search.

The requirement is still deemed proper and is therefore made FINAL.

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:
It does not identify the mailing address of each inventor. A mailing address is an address at which an inventor customarily receives his or her mail and may be either a home or business address. The mailing address should include the ZIP Code designation. The mailing address may be provided in an application data sheet or a supplemental oath or declaration. See 37 CFR 1.63(c) and 37 CFR 1.76.

It does not identify the city and either state or foreign country of residence of each inventor. The residence information may be provided on either an application data sheet or supplemental oath or declaration.

Response to Arguments

Applicant's arguments filed 7/24/2006 with respect to the 35 U.S.C. § 112, First Paragraph rejection (Lack of Enablement) have been fully considered but they are not persuasive.

Applicants argue, *inter alia*, that they have demonstrated the mechanism of action of endostatin and because endostatin is a well-known angiogenesis inhibitor, a molecule that mimics the activity of endostatin would logically also inhibit angiogenesis. Examiner respectfully submits that no demonstration that the claimed compounds mimic the action of endostatin has been demonstrated. All that has been shown is that the claimed compounds bind to either endostatin or the GRGDS motif (Example 3). If the compounds bind to endostatin, thereby inhibiting its interaction with the GRGDS motif, they would effectively function as inhibitors of endostatin activity, not angiogenesis. There is no indication that the claimed compounds actually inhibit angiogenesis *in vivo*, either in the prior art or the instant specification.

Applicants further argue that the examiner has failed to establish why mimics would not work to reduce or prevent angiogenesis. Examiner respectfully submits that, absent any teaching in the prior art or the instant specification, there is no reasonably specific guidance with respect to the particular diseases or conditions applicants intend to treat, nor is there any guidance as to how one would treat any diseases or conditions with the claimed compounds. Even if one accepts the assertion that the claimed compounds are endostatin mimics and act by the same mechanism, applicants have provided no guidance on how one would administer the claimed compounds to treat any and all of the diseases and conditions contemplated by the instant claims.

As such, it would take undue experimentation for one skilled in the art to determine effective doses, administration routes, and administration schedules to treat all of the diseases and conditions encompassed by the instant claims.

Claim Rejections - 35 USC § 112 – First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 3 and 4 are again rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

To be enabling, the specification of the patent application must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557, 1561 (Fd. Cir. 1993). Explaining what is meant by "undue experimentation," the Federal Circuit has stated that:

> The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. PPG v. Guardian, 75 F.3d 1558, 1564 (Fed. Cir. 1996).[1]

[1] As pointed out by the court in *In re Angstadt*, 537 F.2d 498 at 504 (CCPA 1976), the key word is "undue", not "experimentation".

The factors that may be considered in determining whether a disclosure would require undue experimentation are set forth by *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 wherein, citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

1) the quantity of experimentation necessary,

2) the amount of direction or guidance provided,

3) the presence or absence of working examples,

4) the nature of the invention,

5) the state of the prior art,

6) the relative skill of those in the art,

7) the predictability of the art, and

8) The breadth of the claims.

These factors are always applied against the background understanding that scope of enablement varies inversely with the degree of unpredictability involved. *In re Fisher*, 57 CCPA 1099, 1108, 427 F.2d 833, 839, 166 USPQ 18, 24 (1970). Keeping that in mind, the Wands factors are relevant to the instant fact situation for the following reasons:

1. <u>The nature of the invention, state and predictability of the art, and relative skill of those in the art</u>

The claims are drawn to the treatment of a human patient "where angiogenesis inhibition is indicated" (claim 3) and "wherein treatment with endostatin has been indicated" (Claim 4). Thus, the invention relates to the treatment of both known and unknown patient populations. For example, there are likely diseases and pathological conditions susceptible to angiogenesis inhibitors that are not known in the art. Similarly, although endostatin is known to inhibit angiogenesis, it could be indicated in the future for other conditions. Further, in their broadest reasonable interpretation, the claims are also drawn to the treatment of any and all solid tumors since it is known in the art that tumors require angiogenesis to grow.

The relative skill of those in the art is high, generally that of an M.D. or Ph.D. That factor is outweighed, however, by the unpredictable nature of the art. As illustrative of the state of the art, the examiner cites Gura *et al.* (Science, 1997, 278:1041-1042) and Johnson *et al.* (British J. of Cancer, 2001, 84(10):1424-1431).

Gura *et al.*, cited for evidentiary purposes, teaches that researchers face the problem of sifting through potential anticancer agents to find the ones promising enough to make human clinical trials worthwhile and further teach that since formal screening began in 1955, many thousands of drugs have shown activity in either cell or animal models but that only 39 have actually been shown to be useful for chemotherapy (p. 1041, see first and second paragraphs). It is noted that he pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. Also, with regard to unpredictability, Johnson *et al.*, also cited for evidentiary purposes, teach that the *in vivo* activity of 39 different agents in a particular histology in a tumor model did not correlate to activity in the same human cancer. *In re Fisher*, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an

area is, the more specific enablement is necessary in order to satisfy the statute. Further, the mode of action of anticancer agents is often unknown or very unpredictable and administration of such agents is often accompanied by undesirable side effects.

These articles plainly demonstrate that the art of treating cancer, particularly in humans, is extremely unpredictable, particularly in the case of a single compound or genus of compounds being used to treat any and all cancers.

2. The breadth of the claims

The claims are very broad, reciting the treatment of any patient "where angiogenesis inhibition is indicated" (Claim 3) and any patient "wherein treatment with endostatin has been indicated" (Claim 4). In their broadest reasonable interpretation, the claims are inherently drawn to the treatment of any and all solid tumors since it is known in the art that tumors require angiogenesis to grow.

3. The amount of direction or guidance provided and the presence or absence of working examples

The specification provides no direction or guidance for determining the particular administration regimes (dosages, timing, administration routes, etc.) necessary to treat all of the various conditions claimed, particularly in humans. In fact, applicants have provided no examples, working or otherwise, that L-histidine and quisqualic acid can be used to treat any disease or condition or that they even inhibit angiogenesis. All that has been demonstrated is that the claimed compounds bind to either RGD or endostatin. Further, the specification

provides no guidance on experimental methods for determining exactly what conditions are indicated for angiogenesis inhibition.

The working examples are limited to demonstrating that the claimed compounds bind to either RGD or endostatin and thus may be endostatin mimics. There is no evidence in the prior art or in the instant specification that the claimed compounds inhibit angiogenesis or can effectively substitute for endostatin in the treatment of any diseases or conditions. Thus, the applicant at best has provided specific direction or guidance only for assays to determine potential endostatin mimics *in vitro*. No reasonably specific guidance is provided concerning useful therapeutic protocols for any diseases.

4. The quantity of experimentation necessary

Because of the known unpredictability of the art (as discussed *supra*) and in the absence of experimental evidence commensurate in scope with the claims, the skilled artisan would not accept the assertion that the instantly claimed L-histidine and quisqualic acid could be predictably used as treatments for any diseases or conditions as inferred in the claims and contemplated by the specification.

Applicants have failed to provide guidance as to which particular conditions where angiogenesis inhibition or treatment with endoststatin is indicated are contemplated for treatment with L-histidine or quisqualic acid. The skilled artisan would expect the interaction of a particular compound in the treatment of a particular disease state to be very specific and highly unpredictable absent a clear understanding of the structural and biochemical basis for each agent. The instant specification sets forth no such understanding nor any criteria for extrapolating

beyond the *in vitro* laboratory determinations set forth in the specification. No direction is provided for any clinical application. Absent reasonable *a priori* expectations of success for using a particular chemotherapeutic agent to treat any invasive cancer or metastatic tumor or condition wherein angiogenesis inhibition is sought, one skilled in the art would have to extensively test many disease states to discover which respond to a particular compound. Since each prospective embodiment, as well as future embodiments as the art progresses, would have to be empirically tested, undue experimentation would be required to practice the invention as it is claimed in its current scope. The specification provides inadequate guidance to do otherwise.

Accordingly, the instant claims do not comply with the enablement requirement of 35 U.S.C. § 112, first paragraph, since to practice the claimed invention a person of ordinary skill in the art would have to engage in undue experimentation, with no assurance of success.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James D. Anderson whose telephone number is 571-272-9038. The examiner can normally be reached on MON-FRI 9:00 am - 5:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

James D. Anderson, Ph.D.
Patent Examiner
AU 1614

October 6, 2006

Ardin H. Marschel 10/14/06
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SUPERVISORY PATENT EXAMINER